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Clinical and Molecular Cytogenetic Observations in Three Cases of "Trisomy 12p Syndrome"

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Two unpublished cases with partial tandem duplication of 12p and one previously published case were studied by fluorescence in situ hybridization using 11 cosmid DNA probes from 12p. We propose that the smallest duplications of 12(p13.2pter) and 12(p13.1p13.33) produce the "trisomy 12p syndrome" which is characterized by heavy birth weight, macrocephaly, muscular hypotonia, short neck, flat face, high forehead, prominent cheeks, large philtrum, short nose with anteverted nostrils, and broad everted lower lip. From a review of the published cases we conclude that gross malformations are lacking in "pure" trisomy 12p, and mental retardation is severe in complete and moderate in partial trisomy 12p. Polydactyly and accessory nipples were found only with almost complete trisomy 12p. Abnormalities of hair growth may be related to a gene at 12p. The sub-band 12p11.21 may be critical for acrocallosal syndrome. Macrocephaly may be due to a metabolic disorder. © 1996 Wiley-Liss, Inc.

KEY WORDS: **chromosome 12, trisomy 12p, FISH, MA/MR syndrome, acrocallosal syndrome, hypertrophic infant, macrocephaly**

INTRODUCTION

Since Uchida and Lin [1973] reported the first case of trisomy of the short arm of chromosome 12 due to a translocation, at least 25 additional observations have been published [Stengel-Rutkowski et al., 1981 (for review); Qazi et al., 1981; Arnaud et al., 1984; Ray et al., 1985; Rivera et al., 1987]. In all of these cases the duplication of 12p involved a reciprocal translocation and was associated with a deficiency of the various recipient chromosomes. However, "pure" trisomy 12p is present when there is deficiency of the short arm of an acrocentric chromosome which is considered inessential [Armendares et al., 1975; Rethoré et al., 1975; Alfi and Lange, 1977; Biederman et al., 1977; Tenconi et al., 1977; Hansteen et al., 1978; Suerinck et al., 1978; Parslow et al., 1979; Stengel-Rutkowski et al., 1981; Ray et al., 1985]. These cases can be classified together with the observation of a 12p marker chromosome [Kondo et al., 1979] and three cases of tandem duplications [Tayel et al., 1989; Pfeiffer et al., 1992; Leana-Cox et al., 1993]. Although all observations deal with variable duplications of 12p and involve different rearrangements a recognizable "trisomy 12p syndrome" was proposed.

We have studied two new cases of the so far smallest tandem duplications of 12p and reexamined a published observation [Pfeiffer et al., 1992] using 11 DNA probes from 12p. Cases of pure trisomy 12p were reviewed in order to specify karyotype-phenotype correlations.

CLINICAL REPORTS

Case 1 (17116) was published previously [Pfeiffer et al., 1992]. The proposita had a peculiar facial appearance, macrocephaly, agenesis of corpus callosum, severe mental deficiency, a convulsive disorder, preaxial polydactyly (hallux duplex) of both feet, and diabetes insipidus. Her karyotype was 46,XX,inv dup(12)(qter→pter::pter→p11.21::pter) (see Fig. 4a).

At 5½ years the craniofacial appearance is unchanged (Fig. 1). Body length is 111.5 cm, weight is 14.8 kg, and OFC is 53.7 cm. The child is unable to sit without support. Psychomotor retardation is severe. Because of feeding difficulties gastric gavage has become indispensable.

Case 2 (21088) (Fig. 2) was the first child of healthy non-consanguineous parents. At birth paternal age was 35 and maternal age was 30 years. Delivery by cesarean section was at the 38th week of pregnancy. The female infant was hypertrophic (weight 4,510 g, length 55 cm, OFC 36 cm) and she experienced postpartum asphyxia (cord pH 7.0), hypoglycaemia (<10 mg% for 2 hours), persistent fetal circulation with generalised circulation deficiency, cerebral oedema, and renal failure. She recovered after intensive care but developed seizures with "burst-suppression-formations" in the EEG. Ultrasound examination of the brain suggested

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

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Fig. 1. Patient 1 at age $5\frac{1}{2}$ years.

moderate cortical atrophy. A frog-like position and muscular hypertony pointed to disruption of central coordination. Right hydronephrosis due to ureteral stenosis was treated surgically at 3 month. While beta-hydroxy-butyric acid, free fatty acids and lactate were within normal ranges, C-peptide with 6.3 mg/dl (normal <0.3) and insulin with 99 mU/l (normal <13) were elevated. At 9 months a systolic heart murmur was considered represent persistent fetal circulation with open foramen ovale and tricuspid insufficiency. Weight and length were at the 97th centile while the head circumference was below the 3rd centile. She was able to sit up from age of $7\frac{1}{2}$ month, but psychomotor development was considered to be at a 3 to 4 month level. There was partial atrophy of the optic nerve with an estimated vision of 10%.

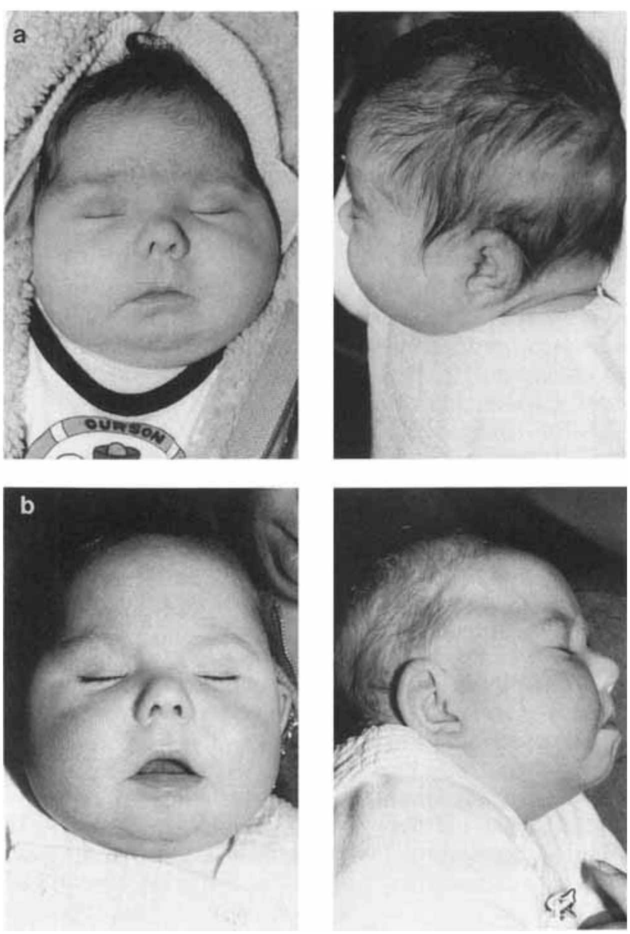

Fig. 2. Patient 2 at age 6 weeks (**a**) and 9 months (**b**).

In addition she had thick cheeks with short upturned nose, short palpebral fissures, and bilateral bridged simian crease. Dermatoglyphics on the left side were W15 R14 U5 U13 U10, on the right W18, R13, R6, U15, U9, with a TRC of 118. Palmar triradii were normally placed. It is noteworthy that connatal long thick hair covering the scalp and the ears disappeared before about age 6 month. Shortly later scalp hair started growing normally.

Lymphocyte karyotype was 46,XX,dir dup(12)(qter→pter::p13.2→pter) (see Fig. 4b). The parents had normal chromosomes.

Case 3 (21549) (Fig. 3) is the second child of non-consanguineous healthy parents. A previous pregnancy resulted in spontaneous abortion. At birth paternal age was 29 and maternal age 31 years. Pregnancy and delivery at the 38th week of pregnancy were unremarkable. Birth weight was 3,100 g and length was 50 cm. Despite mild retardation of speech development early childhood was uneventful. At age 4 years she was socially adapted. While motor development was normal for age, language achievements were limited to three-word sentences. Mild hearing impairment was suspected. Atopic eczema was evident in the popliteal areas. Height, weight, and OFC were at the 50th centile. Inner canthal distance was at the mean while outer canthal distance was below 2SD. There was mild laxity of the small and large joints. She had full cheeks, short upturned nose with hypoplastic alae nasi, short palpebral fissures with mild epicanthus, thin lips, and flat upper lip with a bluish haemangioma. Dermatoglyphics were: left U15 U5 U5 W8 W13, and right U13 U2

Fig. 3. Patient 3 at age 4 years.

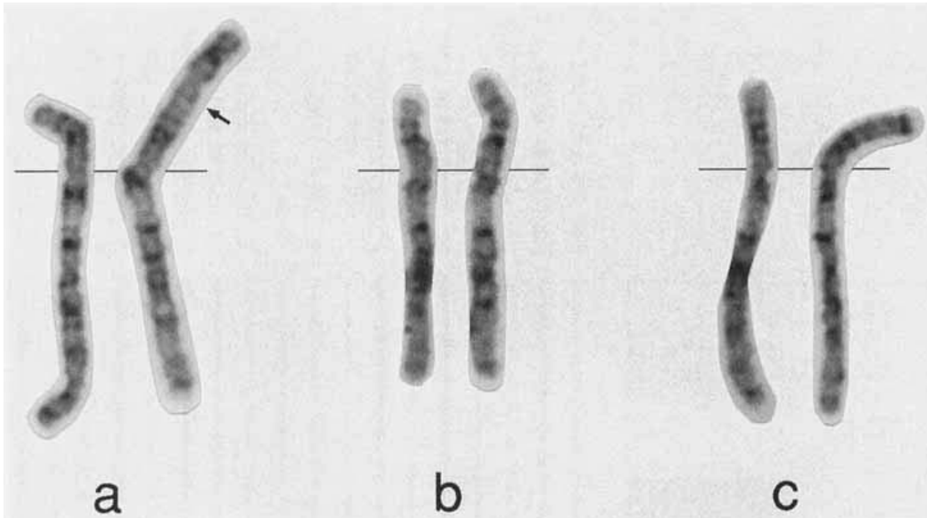

Fig. 4. Pairs of chromosome 12 from patient 1 (**a**), inv dup(12)(pterp11.21); patient 2 (**b**), dir dup(12)(p13.2pter); and patient 3 (**c**), inv dup(12)(p13.33p13.1); at a resolution of 550-850 bands [ISCN, 1995] after GTG banding. Note that there is a GTG-positive band at the distal end of 12p not shown in the ISCN [1995] which produces a dark fusion band (arrow) in case 1(a).

U10 U10 U8 with a TRC of 89. Palmar triradii were distally placed with atd angles of 49° and 53°.

Lymphocyte karyotypes were mosaic 46,XX (10%) 46,XX,inv dup(12)(qter→p13.33::p13.33→p13.1::pter) (90%) (Fig. 4c). Parental chromosomes were normal.

MATERIALS AND METHODS

Peripheral lymphocyte chromosomes were analysed after intercalation of ethidium bromide [Ikeuchi, 1990] and GTG banding.

For FISH studies metaphase and prometaphase lymphocyte spreads were pretreated for 3 min with RNAse (50 ng/ml) and 10 min Pepsin (0.05%). An ATCC chromosome 12 specific library-DNA-probe and the cosmid probes for the loci (cen-tel) D12S934, IAPP, RBTNL2, D12S119, D12S178, PRB3, VWF, FGF6, CACNL1A1, D12S380E, and D12S158 [Chaffanet et al., 1995, kindly provided by Peter Marynen, Leuven] were biotinylated or digoxiginated by Boehringer nick mix or dig mix, respectively. The all-human-telomere probe (Oncor) was mixed with a biotinylated D12Z3 probe (Oncor). After one night's hybridization, detection was attained with FITC-avidin/anti-avidin and anti-digoxigenin-rhodamin (Boehringer) [Lichter et al., 1988].

RESULTS

In all three cases both chromosomes 12 were uniformly painted by a genomic library. The all-human-telomere-probe confirmed presence of normal telomeres in all cases. The results of the 11 cosmid probes from the short arm of chromosome 12 are shown in Table I.

DISCUSSION

Frequent manifestations of pure trisomy 12p (Fig. 5) are summarized in Table II (complete 12p) and Table III (partial 12p). Trisomy 12p produces a recognizable phenotype of unusual facial appearance, increased birth weight, and severe psychomotor retardation occasionally enhanced by postpartum asphyxia. Schinzel [1984] noted that the round faces with prominent cheeks in tri-

TABLE I. Results of FISH Studies With 11 Cosmid Probes From 12p

Patient	1	2	3
Karyotype 46,XX,	inv dup(12) (pterp11.21)	dir dup(12) (p13.2pter)	inv dup(12) (p13.33p13.1)
D12S934	+	+	+
IAPP	++	+	+
RBTNL2	++	+	+
D12S119	++	+	+
D12S178	++	+	++
PRB3	++	++	++
VWF	++	++	++
FGF6	++	++	++
CACNL1A1	++	++	+
D12S380E	++	++	−
D12S158	+	++	−

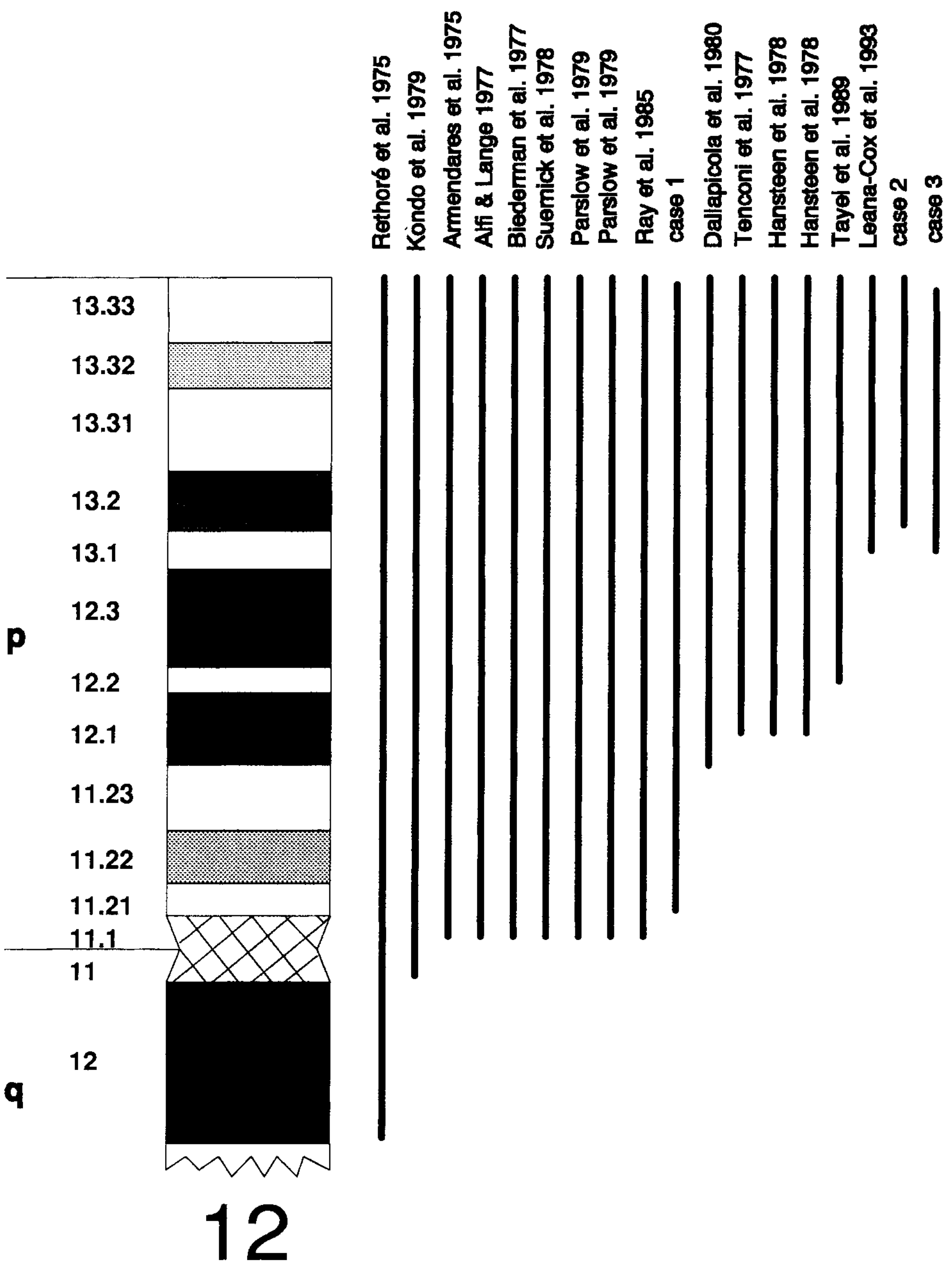

Fig. 5. Ideogramm of 12p [ISCN, 1995] at left shows the size of duplication in the published and in our cases with trisomy 12p. Black lines represent the part of 12p which is duplicated in the aberrant chromosome of pure trisomy 12p patients.

somy 12p syndrome "have some similarity to Down syndrome, particularly in their flatness, midface hypoplasia, shallow orbits, epicanthal folds, flat, wide bridge and upturned tip of the [short] nose and small ears." Further frequent findings were turricephaly with high forehead, long, poorly modeled philtrum, thin upper vermilion, and broad, everted lower lip. The ear abnormalities consists mainly of apparently low set ears with prominent anthelix and deep concha. Foot deformities were present in seven of ten cases, accessory nipples in two of ten cases and polydactyly (feet) in four of ten (Table II). In 12p trisomies with additional chromosomal imbalances the craniofacial anomalies were also evident but might be associated with a major malformation, such as congenital heart defect [Qazi et al., 1981], renal malformation [Rethoré et al., 1975], and anal atresia [Uchida and Lin, 1973], which were not reported in pure trisomies of 12p.

With respect to facial anomalies, high birth weight, foot deformities, and lack of gross malformations there was no difference between the group with complete and with partial trisomy of 12p. The typical appearance was

TABLE II. Frequent Findings in Pure (Complete) Trisomy 12p*

	Kondo, 1979	Rethoré, 1975	Armendares, 1975	Alfi, 1977	Biederman, 1977	Suerinck, 1978	Parslow, 1979	Parslow, 1979	Ray, 1985	Case 1
dup(12)(pter-	q11 mos	q12	p11	p11	p11	p11	p11	p11	p11	p11.21
Sex	m	m	f	f	f	m	f	m	f	f
Weeks of pregnancy	39	37	40	?	38	40	?	41	?	40
Birth weight (g)	3670	3350	4100	?	3680	3250	3400	4050	3100	3630
Turricephaly	−	+	?	?	(+)	+	?	+	?	+
Round face/ prom. cheeks	+	(+)	+	?	(+)	−	−	−	−	+
High forehead	−	+	(+)	+	+	+	+	(+)	+	+
Flat face	+	(+)	++	+	(+)	−	−	+	−	(+)
Epicanthic folds	+	+	+	−	−	−	−	+	+	+
Broad eyebrows	−	−	+	+	−	+	−	−	(+)	−
Broad nasal bridge	+	(+)	+	?	+	−	−	+	+	+
Short nose	+	+	+	+	+	+	+	+	+	+
Anteverted nostrils	+	(+)	+	?	(+)	+	−	+	+	+
Large philtrum	+	+	+	?	(+)	+	+	+	+	+
Thin upper vermilion	−	−	−	+	(+)	+	(+)	+	+	−
Broad everted lower lip	+	+	+	+	−	+	+	+	+	+
Ear anomalies	−	+	+	+	(+)	+	+	+	(+)	+
Short neck	+	+	+	+	+	+	(+)	+	+	+
Polydactyly	+	+	−	+	−	−	−	−	−	+
Accessory nipples	−	−	+	−	+	−	−	−	−	−
Foot deformities	+	?	+	+	+	+	−	−	+	+
Hypotonia	+	+	+	?	+	?	?	+	?	hyper
Development:										
Age of investigation	11 y	10 mo	34 mo		6 m	18 y	10 y	10 mo	15 mo	5½ y
Weight (kg)	3rd	25th	>75th		50th	29	50th	>75th	norm	5th
Lenght/height (cm)	<3rd	50th	25th		50th	130	<3th	<3th	norm	50th
OFC (cm)	97th	>75th	25th	large	97th	52	98th	>50th	norm	97th
Head control at age	6 mo	(+)	8 mo	head	<9 mo	?	Stan-	?	+	−
Sat at age	1 y	−	18 mo		9 mo	?	ford/	−	+	−
Walked at age	−	−	−		?	−	Binet	−	(+)	−
Speech	−	−	?		?	−	0	delay	−	−
Mental retardation	+++	DQ 50	IQ 29	+++	+++	+++	+++	+++	DQ 65	+++

*Kondo et al., 1979; Rethoré et al., 1975; Armendares et al., 1975; Alfi and Lange, 1977; Biederman et al., 1977; Suerinck et al., 1978; Parslow et al., 1979; Ray et al., 1985: MR. +++ severe. norm, normal range; xth, xth centile.

related earlier to a duplication of at least 12(p12pter) [Stengel-Rutkowski et al., 1981]. From our study the critical duplicated segment which manifests even in mosaicism could be narrowed down to 12(p13.1p13.33) [D12S178-FGF6]. However, accessory nipples and polydactyly were not noted in the eight cases of partial trisomy 12p (Table III). Furthermore, the developmental delay in this group was only of moderate degree and mild in our case 3 with mosaicism.

Early death was reported in one patient who died at 13 years of dysgerminoma [Parslow et al., 1979]. A simian/Sydney or other unusual transverse crease was noted in 9 of 11 cases studied. Despite the presence of whorls, a low total ridge count was noted in 5 of 7 patients. There was no consistent distribution of digital patterns; t'' palmar triradii were observed in 4 patients.

By clinical examinations hearing, vision and fundi were considered normal. In one patient only central hearing loss and blindness deduced from evoced potentials was mentioned [Rethoré et al., 1975]. General muscular hypotonia often was associated with feeding difficulties, hernias and cryptorchidism. Failure to thrive was documented by retardation of growth in 6 of 13 patients while weight declined only in 3 patients below the 3rd centile.

The phenotype of patient 1 simulates that of the acrocallosal syndrome of high birth weight, absence of corpus callosum, severe mental retardation, macrocephaly, postaxial polydactyly, and hallux duplication [Pfeiffer et al., 1992]. This AR syndrome has not been mapped so far. The similarity of patients with trisomy 12p and patients with acrocallosal syndrome cannot be overlooked, but it remains unclear if there is one or more genes at 12p the duplication of which causes acrocallosal syndrome, or if the breakpoints disrupted a critical gene. As our patient with agenesis of corpus callosum shared macrocephaly and polydactyly with cases with breakpoints in 12p11, a critical gene could be located in 12p11.21 between D12S934 and IAPP.

Facial hypertrichosis lanugosa congenita was noted only in patient 2 and probably in the patient of Biederman et al. [1977]. So far the origin of hypertrichosis in humans is not well defined, although from a mouse model the FGF5 gene on 4q21 was shown to function as

TABLE III. Frequent Findings in Pure Partial Trisomy 12p*

	Tenconi, 1977	Hansteen, 1978	Hansteen, 1978	Dallapiccola, 1980	Tayel, 1989	Leana-Cox, 1993	Case 2	Case 3
dup(12)(pter-	p12.1	p12.1	p12.1	p12	p12.2	p13.1 mos	p13.2	p13.1 mos
Sex	m	m	m	m	m	m	w	w
Weeks of pregnancy	40	41, 5	40	40	42	40	38	38
Birth weight	3300	3770	3750	2950	3200	?	4510	3100
Turricephaly	+	–	–	?	–	?	–	–
Round face/prom. cheeks	+	+	+	+	–	?	+	+
High forehead	+	(+)	(+)	+	+	?	–	–
Flat face	(+)	+	+	+	–	?	–	–
Epicanthic folds	+	–	–	–	–	?	(+)	(+)
Broad eyebrows	+	–	–	–	–	?	–	–
Broad nasal bridge	+	+	+	+	+	?	+	+
Short nose	+	+	+	+	–	?	+	+
Anteverted nostrils	+	–	+	–	–	?	+	+
Large philtrum	+	+	+	+	–	?	+	+
Thin upper vermilion	+	+	+	(+)	–	?	–	+
Broad everted lower lip	+	+	+	(+)	+	?	+	+
Ear anomalies	+	+	+	+	+	+	(+)	–
Short neck	+	+	+	?	–	?	+	+
Polydactyly	–	–	–	–	–	?	–	–
Accessory nipples	–	–	–	–	–	?	–	–
Foot deformities	+	+	+	–	(+)	?	–	–
Hypotonia	hyper	+	+	+	+	+	hyper	–
Development:								
Age of investigation	26 mo	42 mo	12 mo	12 mo	14 y	?	9 mo	4 y
Weight (kg)	>25th	?	?	?	?	?	97th	50th
Lenght/height (cm)	25th	?	?	?	<3rd	?	97th	50th
OFC (cm)	98th	?	?	?	50th	?	<3rd	<50th
Head control at age	+	+	+	+	12 mo	?	<7 mo	+
Sat at age	+	+	?	11 mo	18 mo	?	7,5 mo	6 mo
Walked at age	+	+	?	(+)	4 y	?	–	12 mo
Speech	+	(+)	?	?	?	?	–	+
Mental retardation	DQ 61	1y l	6mo l	++	IQ 51	?	4mo l	(+)

*Tenconi et al., 1977; Hansteen et al., 1978; Dallapiccola et al., 1980; Tayel et al., 1989; Leana-Cox et al., 1993. xth, xth centile; l, level; MR + mild, ++ moderate, +++ severe.

an inhibitor of hair elongation. As our patient is the only one with facial hypertrichosis, the breakpoint in 12p13.2 between D12S178 and PRB3 might be causative. On the other hand, in patients with tetrasomy 12p sparse scalp hair is common. Therefore, a gene regulating hair growth could be located in 12p.

Microcephaly was present in patient 2 but has never been noted in pure trisomy 12p. Moreover, this abnormality was not present at birth and therefore is probably due to hypoxic-ischemic encephalopathy, rather than the specific duplicated segment or to disruption of a critical gene.

Macrocephaly was noticed in 9 of 13 cases. Of three patients with known OFC at birth, two showed only mild macrocephaly at birth which, however, increased with age. In "trisomy 12p syndrome" macrocephaly is obviously not due to hydrocephaly. We speculate that this abnormality is related to a cerebral abiotrophic disorder or with a metabolic disease because in two cases increasing macrocephaly was observed. Since macrocephaly was mainly seen in patients with complete trisomy 12p and in one patient only with partial trisomy [Tenconi et al., 1977] genes at 12p11 could have a special significance.

Increased enzyme activity of LDHB, TPI and G3PD has been frequently shown in trisomy 12p patients [Rethoré et al., 1975; Biederman et al., 1977; Hansteen et al., 1978; Tenconi et al., 1977, 1978; Serville et al., 1978; Suerinck et al., 1978; Dallapiccola et al., 1980; Hansteen et al., 1978; Pfeiffer et al., 1992] but their impact on metabolism remains unknown. In one patient with intermittent albuminuria an aromatic odor was emphasized [Suerinck et al., 1978]. Hansteen et al. [1978] mentioned inconstantly increased urinary excretion of certain amino acids in one of their patients, which was not noted in their other patient. In our patient 2 who has been large since birth, an increase of insulin and C-peptide in serum was demonstrated. However, further investigations of metabolism in trisomy 12p are needed to clear up these single findings.

High resolution chromosome banding and FISH investigations confirm that chromosome aberrations might be more complex than they seem. As demonstrated in patient 3 there might be a submicroscopic deletion combined with a duplication at the same chromosome. However, more comparable cases are necessary to evaluate the individual significance of clinical findings and chromosome aberration.

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